

Invited Perspective: The Slow Road to Finding Out Whether the “Forever” Chemicals Cause Chronic Disease

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Testicular and kidney cancer are the two cancer types with the strongest evidence for an association with per- and polyfluoroalkyl substances (PFAS), although the literature remains rather sparse for both.^{1,2} The article in this issue of *Environmental Health Perspectives* by Purdue et al.³—which describes testicular cancer among active-duty U.S. Air Force servicemen in relation to PFAS exposure—provides a valuable contribution to the literature.

The authors conducted a relatively large case–control study of 530 individuals with testicular cancer whose cancer was diagnosed during active service (age 18–39 y) and matched controls. Purdue et al. took advantage of serum samples routinely banked for all service members to assess the association of testicular cancer with prediagnostic PFAS serum concentrations. Most of the serum samples were taken shortly after the study participants began their service. For an additional 187 cases and controls, the authors analyzed a second prediagnostic serum sample taken on average 6 y after military service began. First serum samples of PFAS were compared to PFAS serum data from the National Health and Nutrition Examination Survey (NHANES), which reflect levels in the general population, and levels were found to be similar. Second samples were similar to first, and <1% of subjects had fire-fighting jobs, which led to higher exposure. So, in essence, this was a low-exposure population. In their case–control analyses, the authors found a positive trend in risk for testicular cancer by serum perfluorooctanesulfonic acid (PFOS) using the first samples ($p=0.15$) and a more marked monotonic positive trend ($p=0.009$) when analyzing second samples, after adjusting for other PFAS.

The lack of positive trends among the Air Force servicemen for other long-chain legacy PFAS, in particular perfluorooctanoic acid (PFOA), was somewhat surprising. PFOA has previously been linked to testicular cancer, most clearly in prior work near Dupont’s Washington Works plant in West Virginia, where Berry et al.⁴ and Vieira et al.⁵ found strong exposure–response trends. There are two caveats here. First, the number of exposed cases in West Virginia was small (between 10 and 20 in both Barry et al. and Vieira et al., with some overlap of cases), potentially resulting in spurious results. A contrary argument would be that the serum levels of PFOA in West Virginia were much higher than those of the Air Force servicemen, and it is possible that the strong trends in West Virginia depended on very high exposures to PFOA (PFOS was not elevated in the West Virginia drinking water).

Results on PFAS and testicular cancer are sparse in the literature; the cancer is rare and usually not fatal,⁶ and it has not often been studied in relation to PFAS. Most of the existing studies have focused on PFOA. In addition to the two PFOA studies cited above,^{4,5} there was an ecological mortality study with 27 cases also focused on PFOA, but this had a relatively weak design when considering a generally nonfatal disease.⁷ I am unaware of any prior studies specifically of PFOS and testicular cancer. Some mild support for an association between PFOS and testicular cancer comes from a cohort study in Ronneby, Sweden, where drinking water was highly contaminated with PFAS, primarily PFOS and perfluorohexanesulfonic acid (PFHxS).⁸ In residents residing in the “ever high” area (residents of Ronneby supplied by the more contaminated of two water companies), the relative risk for testicular cancer ($n=14$) was 1.28 95% confidence interval: 0.70, 2.15.

There is some limited animal evidence of PFOS toxicity to the testicles. Animals exposed to PFOS have shown delayed maturation of testicular Leydig cells, decreased sperm count, and decreased serum testosterone levels.² Studies have also shown that PFOA, which is closely related chemically to PFOS, causes Leydig cell tumors in rodents.² However, Leydig tumors are very rare in humans.²

In summary, more studies are needed, as is almost always the case for environmental chemicals—in this case, studies of the longer-chain legacy PFAS (PFOA, PFOS, PFHxS) in relation to testicular cancer. Other cohorts with baseline stored serum samples (such as the Air Force servicemen studied here) are one possibility for further study; the legacy PFAS have longer half-lives and will be usually detectable in past serum samples. As a general note, it would be advantageous if the National Institutes of Health were to provide more funding to establish large “exogenous chemical” cohorts similar to those in the Framingham Study,⁹ which may facilitate future studies of low-level background exogenous exposures.

More studies in high-exposure cohorts (to date there are only a few) would also be beneficial; at least one is under way (a collaborative study between the National Cancer Institute and our team of researchers at the Rollins School of Public Health at Emory), conducting further follow-up of cancer incidence in the West Virginia PFOA cohort. Exposure contrasts in high-exposure cohorts may be particularly valuable to detect health effects, although for kidney cancer and PFOA we now have some evidence that effects detectable at low exposure are concordant with effects seen in high-exposure studies.¹⁰

As usual, we are playing catch-up in studying PFAS chemicals that were in the environment for many years before we became concerned about them. Worse yet, these “forever chemicals,” newly created after World War II, do not break down in the environment (microplastics are analogous).² And they are ubiquitous, present in small quantities in the serum of almost everyone—although serum levels are gradually decreasing because production has largely ceased in the United States.² A somewhat surprising consideration is that the pathways via which all of us have been exposed remain somewhat unclear.² We can only hope that the health associations seen to date,

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virtually all of which are not yet definitive regarding chronic disease, do not pan out in the long run.

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